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TITLE: Therapeutic methods utilizing naturally derived bio-active complexes and delivery systems therefor

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PRIOR-ART-DISCLOSED:

## U.S. PATENT DOCUMENTS

☐ Search Selected☐ Search ALL

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
<input type="checkbox"/> <u>4507285</u>	March 1985	Kiihne	424/130
<input type="checkbox"/> <u>4574129</u>	March 1986	Nair et al.	514/540
<input type="checkbox"/> <u>5100661</u>	March 1992	Schmidt	424/85.5
<input type="checkbox"/> <u>5236932</u>	August 1993	Greenfield et al.	514/305
<input type="checkbox"/> <u>5447939</u>	September 1995	Glasky et al.	514/310
<input type="checkbox"/> <u>5451580</u>	September 1995	Murphy et al.	514/212

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PRIMARY-EXAMINER: Criares; Theodore J.

ATTY-AGENT-FIRM: Helfgott &amp; Karas, P.C.

ABSTRACT:

Methods are disclosed for correcting biological information transfer in a patient in need of such therapy which comprise administration to a patient of a composition comprising a therapeutically effective amount of a biocomplex comprising at least one bioactive agent from each of the three informational blocks of biological information transfer, each agent being present in an amount sufficient to correct the biological information transfer of the patient under treatment and resulting in the resumption of normal cell metabolism, said amount being less than the buffering amount of said agent; together with a carrier therefor.

10 Claims, 30 Drawing figures

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## BSPR:

It is necessary to emphasize that such methods utilize the first degree informational substances in amounts greatly exceeding the endogenic production of these substances. For instance, prednisone, a commonly prescribed glucocorticosteroid hormone that is about 6-8 times more active than its endogenous analog hydrocortisone, is typically administered by injection in a dosage of 30 mg or orally, in a daily dosage of 12-16 mg. This is approximately equivalent to 40-60 days of the total production of the adrenal cortex gland (corticosuprarenal gland) of hydrocortisone. Taking into account the activity differential, one typical daily therapeutic dose of prednisone is similar to the amount produced by a normally functioning gland over a period of about ten months.

## BSPR:

Additionally, the physiological and biochemical response from "therapeutic" and "physiological" dosages of bioactive substances are very different. Frequently, unusual and non-physiological effects are observed when the same bioactive substance is used in amounts exceeding the physiological level.

## DRPR:

FIG. 20 is a graph showing the relative amounts of estrogen receptors activity after topical administration of a biocomplex of the instant invention.

## DEPR:

Typical compositions of the instant invention which include steroid-catecholamine biocomplexes utilizable in the therapeutic methods of the present invention typically comprise hydrocortisone (cortisol, preferably water-soluble and balanced with HPBC); corticosterone-21-sulfate (preferably as the potassium salt); progesterone (preferably water-soluble and balanced with HPBC); .beta.-Estradiol, (preferably water-soluble and balanced with HPBC); estriol-3-sulfate sodium salt; cholecalciferol sulfate (Vitamin D3 sulfate); epinephrine hydrochloride (adrenalin); arterenol hydrochloride (Noradrenalin); and aldosterone.

## DEPR:

Typical compositions of the present invention which include protein-peptide biocomplexes which are utilizable in the therapeutic methods of the present invention typically comprise adrenocorticotrophic hormone (ACTH, fragment 1-24); .beta.-lipotropin, .beta.-Endorphin (fragment 61-91); somatotropin (HGH, from human pituitary); follicle-stimulating hormone (FSH, from human pituitary); luteinizing Hormone (LH, from human pituitary); thyrotrophic Hormone (TSH, from human pituitary); vasopressin (arginine vasopressin); parathyroid hormone (fragment 1-36); thyrocalcitonin (calcitonin, from salmon); angiotensin II (human); glucagon (mixture of bovine & porcine); vasoactive Intestinal Peptide (VIP); gastric inhibitory polypeptide (GIP, human); and insulin (human).

## DEPR:

Using corresponding commercial kits, the following hormones have been determined:

DEPU:

1-10 .mu.g somatotropin (HGH, from human pituitary);

DEPU:

2-10 .mu.g progesterone;

DEPU:

1. Adrenocorticoid hormone (ACTH, corticotropin) was determined using the commercial kit ACTHK-PR (CIS International, France) and JNC-2400 (Immuno-Nuckar Corporation, USA);

DEPU:

2. Vasopressin (ADH) was determined using the kits Vasopressin RIA (Buhlman Labor, Switzerland);

DEPU:

3. Lutropin (luteinizing hormone, LH) was determined by means of the kits LH-PR (CIS, France) and RS-4124 (Radioassay System Labor, USA);

DEPU:

4. Follitropin (follicle stimulating hormone FSH) was determined by using the kits FSHK-PR (CIS, France) and RS 4123 (Radioassay System Labor, USA);

DEPU:

5. Somatotropin (STH) was determined by using the kits HgHK (CIS, France) and CNR-722 (Cambridge Medical Diagnostics, USA);

DEPU:

6. Hydrocortisone (hydrocortisone 11, 17, 21, trihydro, 4 pregnen, 3,20-dion) was determined by the commercial kits Cortk-125 (CIS, France) and ING-13170 (Immuno-nuclear Corporation, USA);

DEPU:

7. Aldosterone (11,21-dihydroxy-4 prynal--18 al--11 hemiacetat) was determined by mens of the kits SB-ALDO (CIS, France) and AS-888 (Wien Laboratories, USA);

DEPU:

8. Cyclic adenosine monophosphate (c-AMP, 3'5'-AMP) was determined using the commercial kits TRK-425 (Amersham, England);

DEPU:

9. Cyclic guanosine monophosphate (c-GMP; 3'5'-GMP) was determined by means of the kits TRK-500 (Amersham, England);

DEPU:

10. Renin-angiotensin system was estimated through determining the activity of plasma renin (APR) using the kits RENK (CIS, France);

DEPU:

11. Prostaglandin A(PGA) was determined using the kits CA-501 (Clinical Assay, USA);

DEPU:

12. Prostaglandin E was examined using the kits CA-501 (Clinical Assay, USA) and SG-6001 (Seragen, USA);

DEPU:

13. Prostaglandin F.sub.2.alpha. was determined by means of the kits CA-503 (Clinical Assay, USA) and SG-6002 (Seragen, USA).

DEPV:

1.7 Oligopeptide hormones of the thymus

DEPV:

3.2 Thyroid hormones

## DEPV:

cytosol type of receptors: glucocorticosteroid receptors,  
mineralo-corticosteroid receptors, estrogen receptors, androgen receptors.

## DEPW:

estrogens

## DEPW:

melatonin

## DEPW:

individual receptors for thyroid hormones

## DEPX:

growth hormone (STH; HGH)

## DEPX:

thyroid-stimulating hormone (TSH)

## DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Media Consisting Of: Phosphate
Buffer Ph 7.6	5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.5 g Adrenocorticotrophic
Hormone (ACTH) 50 ng (Fragment 1-24)	.beta.-Lipotropin (.beta.-Endorphin); 4
.mu.g (Fragment 61-91)	<u>Somatotropin (HGH)</u> 10 miu (from human pituitary) =5 .mu.g
Follicle-Stimulating Hormone (FSH) 0.5 iu (from human pituitary)	=0.07/.mu.g
Luteinizing Hormone (LH) 0.5 iu (from human pituitary)	=0.1 .mu.g Thyrotropic
Hormone (TSH) 0.5 miu (from human pituitary)	=0.071/.mu.g Vasopressin 20 ng
(Arginine Vasopressin) =0.7 .mu.l	Parathyroid Hormone 0.65 .mu.g (Fragment 1-36)
Thyrocalcitonin, (Calcitonin) 20 ng (from Salmon)	Angiotensin II 5 ng Human
Glucagon 40 .mu.g (Mixture of Bovine & Porcine)	Vasoactive Intestinal Peptide
(VIP) 40 ng Gastric Inhibitory Polypeptide (GIP) 100 ng (Human)	Insulin 16 miu
(Human) =0.6666 .mu.g	Delivery system of Example A 26.14 g

## DETL:

	Ingredient Amount/1 kg Cream
	Aqueous Media Consisting Of: Phosphate
Buffer pH 7.6	5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.4 g Bioactive Agents:
Hydrocortisone (Cortisol) 75 .mu.g (water-soluble; balanced with HPBC)	
Corticosterone - 21-sulfate; 1.8 .mu.g	Potassium Salt <u>Progesterone</u> 6 .mu.g
(water-soluble; balanced with HPBC)	.beta.-Estradiol 100 ng (water-soluble;
balanced with HPBC)	Estriol-3-Sulfate Sodium salt 70 ng Cholecalciferol Sulfate
(Vitamin D3 500 .mu.g sulfate)	Epinephrine hydrochloride 200 ng (Adrenalin)
Arterenol hydrochloride 200 ng (Noradrenalin)	d-Aldosterone-21-Hemisuccinate 125
ng	Delivery system of Example A 26.14 g

## DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Media Consisting Of: Phosphate
Buffer pH 7.6	5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.5 g Bioactive Agent:
Adrenocorticotrophic Hormone (ACTH) 110 .mu.g (Fragment 1-24)	.beta.-Lipotropin
(.beta.-Endorphin); 6 .mu.g (Fragment 61-91)	<u>Somatotropin (HGH)</u> 10 miu =5 mg
Follicle-Stimulating Hormone 0.5 iu (FSH) =0.071/.mu.g	Luteinizing Hormone (LH)
0.5 iu (from human pituitary) =0.1 .mu.g	Thyrotropic Hormone (TSH) 0.75 miu
=0.1071/.mu.g	Vasopressin 15 mg =0.525 .mu.l
(Fragment 1-34)	Parathyroid Hormone 1.0 .mu.g
	Vasoactive Intestinal Peptide (VIP) 60 ng Insulin 24 miu =1.0
	.mu.g Delivery system of Example A 26.14 g

## DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Media Consisting of: Phosphate

Buffer pH 7.6 5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.4 g Bioactive Agents:  
 Hydrocortisone 75 .mu.g (water-soluble; balanced with HPBC)  
 Corticosterone-21-Sulfate 1.8 .mu.g Progesterone 7.2 .mu.g (water-soluble;  
 balanced with HPBC) .beta.-Estradiol 50 ng (water-soluble; balanced with HPBC)  
 Estriol-3-Sulfate Sodium Salt 40 ng Cholecalciferol Sulfate 1000 .mu.g (Vitamin  
 D3 Sulfate) Epinephrine hydrochloride 50 ng (Adrenalin) Arterenol hydrochloride  
 50 ng (Noradrenalin) d-Aldosterone-21-Hemisuccinate 200 ng Delivery system of  
 Example A 26.14 g

DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Consisting of: Phosphate Buffer
pH 7.6 5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.5 g Bioactive Agents:	
Adrenocorticotrophic Hormone (ACTH) 155 ng (Fragment 1-24) .beta.-Lipotropin	
(.beta.-Endorphin); 8 mg (Fragment 61-91) <u>Somatotropin</u> (HGH) 10 miu =5 mg	
Follicle-Stimulating Hormone 0.5 iu (FSH) =0.071/mg Luteinizing Hormone (LH) 0.5	
iu =0.1 mg Thyrotrophic Hormone (TSH) 1.0 miu =0.1428/mg Vasopressin 15 ng =0.525	
ml Parathyroid Hormone 1.5 .mu.g (Fragment 1-34) Vasoactive Intestinal Peptide	
(VIP) 80 ng Insulin 30 miu =1.25 mg Delivery system of Example A 26.16 g	

DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Media Consisting Of: Phosphate
Buffer pH 7.6 5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.4 g Bioactive Agents:	
Hydrocortisone 75 .mu.g (water-soluble; balanced with HPBC)	
Corticosterone-21-Sulfate 1.8 .mu.g <u>Progesterone</u> 7.2 .mu.g (water-soluble;	
balanced with HPBC) .beta.-Estradiol 30 ng (water-soluble; balanced with HPBC)	
Estriol-3-Sulfate Sodium Salt 20 .mu.g Cholecalciferol Sulfate 1500 .mu.g	
(Vitamin D3 Sulfate) Epinephrine hydrochloride 25 ng (Adrenalin) Arterenol	
hydrochloride 25 ng (Noradrenalin) .tau.-Aldosterone-21-Hemisuccinate 250 ng	
Delivery system of Example A 26.16 g	

DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Media Consisting Of: Phosphate
Buffer pH 7.6 5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.5 g Bioactive Agents:	
<u>Somatotropin</u> (HGH) 10 miu = 5 .mu.g Follicle-Stimulating Hormone 0.4 iu = 0.057/	
.mu.g (FSH) Luteinizing Hormone (LH) 0.4 iu = 0.08 .mu.g Vasopressin 25 ng =	
0.875 .mu.l Thyrocalcitonin (Calcitonin) 130 ng (from Salmon) Angiotensin 12 ng	
Glucagon 150 .mu.g Vasoactive Intestinal Peptide 20 ng (VIP) Gastric Inhibitor	
Peptide 375 ng Lipase, Type I 50 mg (from Wheat Germ) Lipase, Type XI 10,000	
Units Heparin Sodium Salt 4,000 Units = 28.6 mg (Grade II)	

DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Media Consisting Of: Phosphate
Buffer pH 7.6 5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.4 g Bioactive Agents:	
Hydrocortisone 75 .mu.g (water-soluble; balanced with HPBC)	
Corticosterone-21-Sulfate 1.8 .mu.g <u>Progesterone</u> 3 .mu.g (water-soluble;	
balanced with HPBC) .beta.-Estradiol 200 ng (water-soluble; balanced with HPBC)	
Estriol-3-Sulfate Sodium salt 150 ng Epinephrine hydrochloride 600 ng	
(Adrenalin) Arterenol hydrochloride 825 ng (Noradrenalin)	
d-Aldosterone-21-hemisuccinate 60 ng Delivery system of Example A 26.14 g	

DETL:

	Ingredient Amount 1/kg Cream
	Aqueous Media Consisting Of: Phosphate
Buffer pH 7.4 5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.5 g Bioactive Agents:	
<u>Somatotropin</u> (HGH) 10 miu = 5 .mu.g Follicle-Stimulating Hormone (FSH) 0.4 iu =	
0.057/ .mu.g Luteinizing Hormone (LH) 0.4 iu = 0.08 .mu.g Vasopressin 25 ng =	
0.875 .mu.l Thyrocalcitonin (Calcitonin) 160 ng (from Salmon) Angiotensin 16 ng	
Glucagon 180 .mu.g Vasoactive Intestinal Peptide (VIP) 20 ng Gastric Inhibitor	

Peptide 425 ng Lipase, Type I 80 mg Lipase, Type XI 15,000 Units Heparin Sodium Salt 6,000 Units = 42.3 mg (Grade II) Delivery system of Example A 26.14 g

## DETL:

Ingredient Amount 1/kg Cream  
Aqueous Media Consisting Of: Phosphate buffer pH 7.6 5.0 ml Hydroxypropyl-.beta.-Cyclodextrin 0.4 g Bioactive Agents: Hydrocortisone 75 .mu.g (water-soluble; balanced with HPBC) Corticosterone-21-Sulfate 1.8 .mu.g Progesterone 2.0 .mu.g (water-soluble; balanced with HPBC) .beta.-Estradiol 300 ng (water-soluble; balanced with HPBC) Estriol-3-sulfate Sodium salt 200 ng Epinephrine hydrochloride 750 ng (Adrenalin) Arterenol hydrochloride 1050 ng (Noradrenalin) d-Aldosterone-21-hemisuccinate 60 ng Delivery system of Example A 26.14 g

## DETL:

Ingredient Amount 1/kg Cream  
Phosphate Buffer, pH 7.4 1.5 ml HPBC 1 g Protein Peptides h-GH (somatotropin) 10 mIU = 5 .mu.g VIP (vasoactive Intestinal 0.02 .mu.g Polypeptide GIP (Gastric Inhibitor Polypeptide) 0.375 .mu.g Glucagon 150 .mu.g Thyrocalcitonin; from salmon 0.15 .mu.g (calcitonin) Arg-Vasopressin; Aqueous Solution 0.875 ml = 0.023 .mu.g Angiotensin II; Human 0.012 .mu.g Lipase, Type XI 10,000 units = 0.025 mg Lipase, Type I 50 mg Heparin Sodium Salt 4,000 units = 28.6 mg

## DETL:

Ingredient Amount 1kg/cream  
Part A Aqueous media consisting of 2.25 ml Phosphate Buffer, pH 7.4 HPBC 1.5 g Steroids Hydrocortisone - Water Soluble 0.75 mg (Balanced in 2-HPBC) Act.: 0.075 mg Corticosterone-21-Sulfate Potassium Salt 0.0018 mg d-Aldosterone-21-Hemisuccinate 0.00006 mg .beta.-Estradiol-Water Soluble 0.0044 mg (Balanced in 2-HPBC) Act.: 0.003 mg Estriol-3-Sulfate Sodium Salt 0.00015 mg Progesterone-Water Soluble 0.043 mg (Balanced in 2-HPBC) Act: 0.003 mg Part B 1N HCl 0.2 ml Epinephrine Hydrochloride (Adrenalin) 0.0006 mg Arterenol Hydrochloride (Norodrenlin) 0.00083 mg Part C Ethyl Alcohol 0.75 ml .alpha.-Tocopherol Acetate (Vit E) act: 1360 IU/g 30 mg Ergocalciferol (Vitamin D.sub.2) act: 1 mg 4 .times. 10.sup.6 USP/g Retinol Palmitate (Vit A): dispersed in 60 mg gelatin matrix

## DETL:

Ingredient Amount 1 kg/cream  
Phosphate Buffer, pH 7.4 1.5 ml HPBC 0.725 mmol 1 g h-GH (Somatotropin) 8 mIU = 4 .mu.g .beta.-Endorphin (.beta.-Lipotropin) .mu.mg VIP (Vasoactive Intestinal Polypeptide) 0.12 mg Insulin 35 mIU = 1.4 .mu.g PTH (Parathyroid Hormone) 0.8 .mu.g Vasopressin 1.75 ml = 0.05 .mu.g

## DETL:

Part A Solvent Phosphate Buffer, pH 7.4  
1.5 ml HPBC 0.725 mmol 1 g Steroids  
Ingredient Amount 1 kg/cream  
Hydrocortisone-Water Soluble 0.75 mg (Balanced in 2-HPBC) Act: 0.075 mg Corticosterone-21-Sulfate Potassium 0.0018 mg Salt d-Aldosterone-21-Hemisuccinate 0.0005 mg .beta.-Estradiol-Water Soluble 0.0033 mg (Balanced in 2-HPBC) Act.: 0.00015 mg Estriol-3-Sulfate Sodium Salt 0.0001 mg Progesterone-Water Soluble 0.171 mg (Balanced in 2-HPBC) Act: 0.0012 mg Part B Solvent Ethyl Alcohol 0.25 ml Oil Soluble Vitamins Ingredient Amount 1 kg/cream Ergocalciferol (Vitamin D.sub.2) 2 mg Act: 4 .times. 10.sup.6 USP/g Cholecalciferol Sulfate Sodium Salt 0.6 mg .alpha.-Tocopherol Acetate (Vitamin E) 30 mg Act: 1360 IU/g

## DETL:

Ingredient Amount 1 kg/cream  
Aqueous media comprising: Phosphate

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Buffer 1.5 ml HPBC 0.725 mmol 1 g \_\_\_\_\_  
Ingredient Amount 1 kg/cream \_\_\_\_\_ h-GH  
(Somatotropin) 14 mIU = 7 .mu.g .beta.-Endorphin (.beta.-Lipotropin) 6 .mu.g VIP  
(Vasoactive Intestinal Polypeptide) 0.15 .mu.g Insulin 54 mIU = 2.16 .mu.g PTH  
(Parathyroid Hormone) 1.3 .mu.g Vasopressin 3 ml = 0.086

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Steroid-Vitamin Biocomplex for Eye Zone  
Part A Aqueous media consisting of: Phosphate Buffer, pH 7.4 1.8 ml HPBC 1.2 g  
Ingredient Amount 1 kg/cream  
Hydrocortisone-Water Soluble 0.75 mg  
(Balanced in 2-HPBC) Act: 0.075 .mu.g Corticosterone-21-Sulfate Potassium 0.0018  
mg Salt d-Aldosterone-21-Hemisuccinate 0.0005 mg .beta.-Estradiol-Water Soluble  
0.0033 mg (Balanced in 2-HPBC) Act.: 0.00015 mg Estriol-3-Sulfate Sodium Salt  
0.0001 mg Progesterone-Water Soluble 0.171 mg (Balanced in 2-HPBC) Act: 0.0012  
mg  
Part B Ethyl Alcohol 0.3 ml  
Ergocalciferol (Vitamin D.sub.2) 3 mg Act: 4 .times. 10.sup.6 USP/g  
Cholecalciferol Sulfate Sodium Salt 0.6 mg (Vitamin D.sub.3) .alpha.-Tocopherol  
Acetate (Vitamin E) 60 mg (Act: 1360 IU/g \_\_\_\_\_

## DETL:

Ingredient Amount/Usage Per Dose  
Phosphate Buffer 1 ml HPBC  
(Hydroxypropyl-.beta.-Cyclodextrin) 0.2 g Adrenocorticotrophic Hormone 0.5-2.5 ng  
(Fragment 1-24) .beta.-Endorphin 0.04-0.1 ng (Fragment 61-91) Somatotropin  
(B-GH) 0.05-0.1 ng Thyrotrophic Hormone (TSH) 0.005-0.01 mIU Vasopressin  
(Arginine Vasopressin) 0.2-2 ng Thyrocalcitonin 0.2-1 ng Angiotensin II 0.1-3 ng  
Insulin 0.15-1 mIU \_\_\_\_\_

## CLPR:

3. The composition according to claim 1 also comprising: adrenocorticotrophic hormone; .beta.-lipotropin; .beta.-endorphin; somatotropin; follicle-stimulating hormone; luteinizing hormone; thyrotrophic hormone; vasopressin; parathyroid hormone; thyrocalcitonin; angiotensin II; glucagon; vasoactive intestinal peptide; gastric inhibitory polypeptide; or insulin.

## CLPR:

5. The composition according to claim 1 also comprising: hydrocortisone; corticosterone-21-sulfate; progesterone; .beta.-estradiol; estriol-3-sulfate sodium salt; cholecalciferol sulfate; epinephrine hydrochloride; arterenol hydrochloride; or aldosterone.

## CLPV:

1-10 .mu.g somatotropin;

## CLPV:

2-10 .mu.g progesterone;

## CLPV:

wherein the composition further comprises a protein-peptide biocomplex bioactive agent comprising: adrenocorticotrophic hormone; .beta.-lipotropin .beta.-endorphin; somatotropin; follicle-stimulating hormone; luteinizing hormone; thyrotrophic hormone; vasopressin; parathyroid hormone; thyrocalcitonin; angiotensin II; glucagon; vasoactive intestinal peptide; gastric inhibitory polypeptide; insulin; or mixtures thereof;

## CLPV:

wherein the composition further comprises a second bioactive agent comprising: hydrocortisone; corticosterone-21-sulfate; progesterone; .beta.-estradiol; estriol-3-sulfate sodium salt; cholecalciferol sulfate epinephrine hydrochloride; arterenol hydrochloride; aldosterone and mixtures thereof; or